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In re Application of: **Behan, D. et al.**
Serial No.: **09/060,188**
Filed: **April 14, 1998**

For: **A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful In The Treatment of Disease**
Examiner: **Basi, N.**
Attention: **Art Unit 1646**

**In the United States Patent and Trademark Office**

In re Application of: **Behan, D. et al.**
Serial No.: **09/060,188**
Filed: **April 14,1998**
Art Unit:**1646**
Examiner: **Basi, N**

**A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful In The Treatment of Disease**

Director of Patents and Trademarks
Washington, D.C. 20231

**HAND-DELIVERY RECEIPT**

Dear Sir:

Applicants' representative would like to thank the Examiner for agreeing to an interview on **February 13, 2001 at 2pm** to discus U.S. Patent application numbers **09/060,188** and **09/170,496**.

The following documents relating to application 09/060,188 are being **hand delivered** by the undersigned as a **Courtesy Copy**. The Examiner has indicated that the Response attached hereto is still in the docketing department. Because this Response is filled with numerous examples and a declaration by a well respected scientist in the art, that in turn addresses each and every point raised by the Office, Applicants send this copy directly to the Examiner allowing the Examiner ample time to review the information provided therein.

Perhaps a good starting point for discussion during the interview might be the declaration by Stanley J. Watson, M.D., Ph.D. Dr. Watson is currently a Professor & Research Scientist in the Department and Mental Health Research Institute at the University of Michigan. Dr. Watson is Board Certified in Psychiatry and Neurology and has been on the Editorial Boards of several scientific journals. In the alternative, a discussion could commence with the application of commercially available techniques, well known in the art, with orphan G protein coupled receptors as a means of deducing the receptor's function. However, I leave this up to your discretion.

The items contained herein were filed on **November 13, 2000**, as evidenced by the official PTO date stamp affixed hereto.

1) **Response to Official Action Dated May 10, 2000 ("Response")**
The Response includes Appendix A through I, each separated by "blue sheets" and the following documents:
   (a) Declaration of Stanley J. Watson, M.D., Ph.D. (including Appendix A; Appendix B (B1-B3); Appendix C; Appendix D (D1-D2), each separated by "green sheets".

(b) Formalized Figure 12.

(c) Sealed Envelope Titled, "Proprietary Material Not Opened to the Public. To Be opened only By Examiner or Other Authorized Patent And Trademark Office Employee".

(d) In re Oetiker, 977 F.2d 1443 (Fed. Cir. 1992).

(e) Written Description Guidelines and Utility Guidelines, Kunin, S.G., 82 *JPTOS* 77 (2000).

(f) G protein-coupled receptors in silico, Horn, F. et al., 76 *Mol. Med.* 464 (1998).

(g) Use of Constitutive G Protein-Coupled Receptor Activity for Drug Discovery, Chen, G. et al., *Mol. Pharm.* 57:125-134 (2000).

(h) Analysis of large gene databases for discovery of novel therapeutic agents, Browne, M.J., *J. Biotechnology* 247 (2000).

(i) Orphan receptors, novel neuropeptides and reverse pharmaceuticals research, Civelli O. et al., 848 (1-2) *Brain Res* 63 (1999).

(j) Constitutively active receptors as a disease-causing mechanism, Parma, J. et al., 100 *Mo. Cell. Endocrin.* 159 (1994).

2) **Authorization of Power of Attorney**
Authorization of Power of Attorney for Ann A. Nguyen filed herewith.

3) **Revocation of Power of Attorney**
Copy of Revocation of Power of Attorney for Laurence Weinberger and Power of Attorney or Authorization of Agent both filed on October 14, 1999.

4) **Request for Three Month Extension**

(a) Petition for Extension of Time Under 37 C.F.R. 1.136(a) ("Petition")

(b) Authorization to charge any fees or credit any overpayment to Deposit Account Number **50-1441**

(c) Duplicate Copy of the Petition

Dated: January ___, 2000

I hereby certify that the above-listed documents were **HAND DELIVERED** on the date indicated above to the following location at the United States Patent & Trademark Office:

By: _____
Name (print)

**Delivered to:**

**Art Unit:** _____

**Recipient Name:** _____

**PTO Date Stamp acknowledging receipt of the foregoing:**

Attorney Docket No.: AREN-0039

**In the United States Patent and Trademark Office**

In re Application of: **Behan, D. et al.**
Serial No.: **09/060,188**
Filed: **April 14,1998**
Art Unit:**1646**
Examiner: **Basi, N**

**A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful In The Treatment of Disease**

Director of Patents and Trademarks
Washington, D.C. 20231

**TRANSMITTAL LETTER**

Dear Sir:

The material contained in the envelope labeled "Proprietary Material" are materials considered to be proprietary and are being submitted herewith for consideration under MPEP §724. A petition under 37 C.F.R §1.182 and fee therefore to expunge the information, if found *not* to be important to a reasonable examiner in deciding whether to allow the application to issue as a patent, is also submitted herewith.

Respectfully submitted,

Date: November 13, 2000

Ann A. Nguyen
USPTO Reg. No. 46,087

COPY

Attorney Docket No.: AREN-0039

**In the United States Patent and Trademark Office**

In re Application of: **Behan, D. et al.**
Serial No.: **09/060,188**
Filed: **April 14,1998**
Examiner: **Basi, N**
Attention: **Art Unit 1646**

**A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful In The Treatment of Disease**

Director of Patents and Trademarks
Washington, D.C. 20231

**PETITION TO EXPUNGE PROPRIETARY MATERIAL UNDER 37 CFR 1.182**

Dear Sir:

This is a request under the provisions of 37 C.F.R §1.182 to expunge the proprietary information enclosed in the sealed enveloped labeled "Proprietary Material Not To Be Open To The Public". The requested expunction and appropriate fee is $130.00. The Commissioner is hereby authorized to charge **$130.00** which is required, or credit any overpayment, to Deposit Account Number 50-1441. I am the agent of record of the entire interest.

Respectfully submitted,

Date: November 13, 2000

Ann A. Nguyen
USPTO Reg. No. 46,087

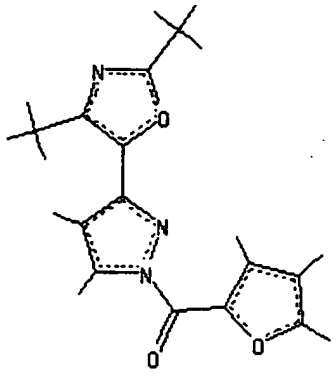
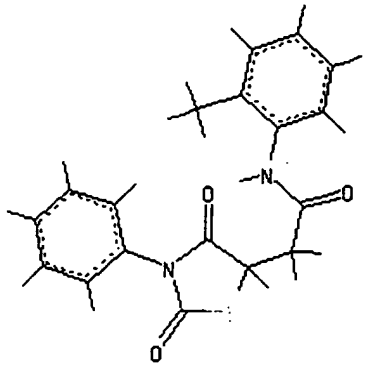
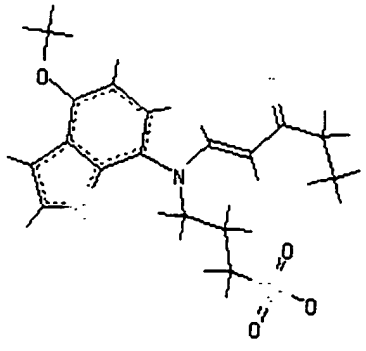
COPY

# Appendix H

| Arena Code Name | Public Name |
|---|---|
| 19AJ | RUP3* |
| 18F | GPR6 |
| 19Y | RE2 |
| 18A | GPR1 |
| 18AI | GPR32 |
| 19BX | Mas1 |
| 19M | ETBR-LP2 |

* 19AJ is believed to be a novel receptor discovered by Arena which patent application has been filed on October 12, 1999 having the serial number 09/417,044.

Appendix H con'td

| Compound Code | Compound Structure |
|---|---|
| Cmd A |  |
| Cmpd 1 |  |
| Cmpd 2 |  |

**In the United States Patent and Trademark Office**

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Serial No.: **09/060,188**
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**A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful In The Treatment of Disease**

Director of Patents and Trademarks
Washington, D.C. 20231

San Diego, California
November 13, 2000

**RESPONSE TO OFFICIAL ACTION DATED MAY 10, 2000**

Dear Sir:

This is in response to the Office Action mailed on May 10, 2000, whereby a response to such Action, with a three month extension of time request, is due on Friday, November 10, 2000. According to MPEP§710.05, when a Federal Holiday falls on a Saturday, the preceding day, Friday, is considered to be a Federal Holiday. Saturday, November 11, 2000 was Veteran's Day, which was observed in the District of Columbia on Friday, November 10th. Therefore, Friday November 10, 2000 is considered a Federal Holiday. Accordingly, any action taken on the next succeeding business day, Monday November 13, 2000 is considered timely. This Response is being filed on November 13, 2000 and is therefore timely.

A three-month extension of time to respond to the Office Action is being requested herewith. Authorization to charge $445.00 from Account No. 50-1441 for such extension is enclosed herewith. Applicants request review of the following and reconsideration of the issues raised by the Office in the Action in light of the points and information provided herein.

Date: November 13 2000

I hereby certify that this paper is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231. A self-addressed, stamped post-card is also enclosed herewith.

Ann A. Nguyen
U.S. Reg. No.: 46,087

COPY

Applicants note that a Revocation of Power of Attorney for Laurence Weinberger and a Power of Attorney or Authorization of Agent were simultaneously filed with the Office on October 14, 1999. For convenience, Applicants have submitted a copy of these two documents. However, communications from the Office appear to continue to be sent to Mr. Weinberger. In addition, a second Power of Attorney or Authorization of Agent is submitted herewith authorizing Ann A. Nguyen to represent Applicants as their Agent. All future communications in this case should be mailed to the following:

Ann A. Nguyen
Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121
Telephone: (858) 453-7200 x294
Facsimile: (858) 453-7210

## Remarks

### I. Summary of Office Action

Applicants confirm that the Office has received and made of record the Response to Office Action ("Response") filed on February 16, 2000. Applicants further note that rejections under 35 U.S.C. 112, second paragraph, have been withdrawn in light of Applicants' Response.

This is the second substantive examination of the claims in this case. Claims 1-18, 33-34 and 39-40 are pending. All pending claims have been rejected under the provision of 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph based upon certain guidelines recently promulgated by the Office. No claim has been rejected under any provisions of Sections 102 or 103. As will be set forth below, all pending claims comply with sections 101 and 112, first paragraph.

In response to this Office Action, Applicants have also submitted a new formal drawing for Figure 12. New formal drawings are believed to be in conformance with 37 C.F.R. §1.84.

### II. Revised Utility Guidelines

Prior to addressing the points raised by the Office and for purposes of clarity, a brief discussion of the recently promulgated guidelines is provided.

The utility guidelines were recently revised to include an additional standard for establishing whether a claimed invention provides proper utility. This new guideline shifted from originally requiring the claims to provide *any* specific utility that is credible to a specific *and* substantial utility

that is credible *or* which provides a well-established utility. These revisions did away with "throw away" utilities because, according to the Office, such utilities were not specific and substantial. Thus, without a doubt, the revised guidelines de facto raise the bar for compliance for utility under Section 101. The guidelines were published in the Federal Register on December 21, 1999 and are awaiting to be finalized. As the guidelines indicate, they have been promulgated to assist Office personnel in their review of applications for compliance with the utility requirement under Section 101.

Applicants note, for context, that "utility" under Section 101 is always assessed from a "minimal" perspective. Almost *any* evidence of utility (excluding "throw away" utilities) is sufficient under Section 101. The guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112, nor are they designed to obviate the examiner's review of applications for compliance with all other statutory requirements for patentability. *See*, 40 Fed. Reg. 244, 71441 (1999). Nevertheless, as with any new rule, as the parameters of the rule become defined, the potential for misapplication of a new rule, despite assurances to the contrary, must be considered as possible.

To summarize, the revised guidelines require that a claimed invention provide a specific *and* substantial utility that is credible, or the claimed invention must provide a well established utility that is immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The Office has rejected claims 1-18, 33-34 and 39-40 under 35 U.S.C §101 because the claimed invention is allegedly not supported by either a specific *and* substantial asserted utility or a well established utility. However, the Office concedes and admits that the asserted utility provides a specific utility. As will be established below, Applicant's claimed invention provides both a specific *and* substantial utility, and based upon the Specification and with the knowledge of one skilled in the art, a well established utility.

## III. Summary of the Claims

Claims 1-18, 33-34 and 39-40 are pending in this application. Claims 1-18 are directed to a method of directly identifying compounds having inverse agonist or agonist activity to a constitutively activated orphan receptor. The claimed method comprises the steps of contacting the compound with a constitutively activated receptor, determining, by measuring the compound efficacy, whether a compound is an inverse agonist or an agonist to the receptor and directly identifying if the compound inhibits (*i.e.*, is an inverse agonist) or activates (*i.e.*, agonist) the receptor functionality.

Claims 33-34 and 39-40 are directed to methods for identifying compounds having inverse agonist or agonists activity at non-endogenous constitutively activated G protein coupled cell surface orphan receptors (in the case of claims 33-34) and at endogenous constitutively activated G protein coupled cell surface orphan receptors (in the case of claims 39-40).

## IV. Procedure for Review of Response

In evaluating the patentability of an application, the Office has the initial burden of presenting a prima facie case and providing evidentiary support of unpatentability. The Court of Appeals for the Federal Circuit indicated in In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, (Fed. Cir. 1992), that a "prima facie case is a procedural tool of patent examination, allocating the burdens of going forward as between examiner and applicant." Oetiker at 1445; *see also* MPEP §2107.01(f)(i) Consideration of a Response to a Prima Facie Rejection For Lack of Utility. The Court further stated, "[a]fter evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." Oetiker at 1445. A "preponderance of the evidence" is a standard of proof by which evidence for one position is of greater weight or more convincing than the evidence which is offered in opposition, and as a whole shows that the fact sought to be proved is more probable than not. *See*, Black's Law Dictionary, Sixth Edition. In a comparative sense, once the Office presents its position to establish a prima facie case, an applicant must provide evidence in response; if, on balance, the applicant's evidence is not counterbalanced by evidence presented by the Office, the rejection can not be sustained. The word "evidence" thus becomes key to this analysis: when an applicant provides: facts; data; declarations by experts; third party references; etc. in rebuttal to a rejection, if the Office does not provide equal or greater evidence to rebut applicant's position, than the applicants have prevailed by a preponderance of evidence and the rejection must be withdrawn.

In a recent article written by Stephen Kunin, the Deputy Assistant Commissioner for Patent Policy and Projects, Deputy Assistant Commissioner Kunin discussed the newly implemented Written Description Guidelines and Utility Guidelines. *See*, Kunin, S., 82 J. Pat. & Trademark Off. Soc'y 77 (2000). For this purpose, Applicants draw particular attention to Deputy Assistant Commissioner Kunin's discussion on the new Utilitly Guidelines and the procedures to be taken by the Office when reviewing patent applicants for compliance with the new "substantial" utility guidelines. Deputy Assistant Commissioner Kunin summarized the steps required to be taken by the Office as follows:

1. Read the claims and the written description to ascertain what has been claimed and whether the claims define a statutory subject matter.

2. Determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible. However, if there is a well-established utility, no rejection under section 101 should be made.

3. If the Office determines that the claimed invention provides neither a specific, substantial utility that is credible nor a well-established utility, the Office should reject the claimed invention under §101. Further, the Office should reject the claimed invention under §112, first paragraph for failure to disclose how to use the claimed invention.

4. Once the Office has established prima facie showing of no specific and substantial credible utility, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by providing in the form of a declaration under 37 C.F.R. §1.132 or a printed publication that rebuts the prima facie case by showing that the claimed invention has a specific and substantial utility that is credible or by showing a well-established utility for the claimed invention.

*See*, 82 JPTOS at 94-95 (2000).

In addition to Deputy Assistant Commissioner Kunin's discussion on proper Office personnel protocol in these matters, in his position as Deputy Assistant Commissioner for Patent Policy and Projects, Deputy Assistant Commissioner Kunin makes clear how the Office must treat statements made by the applicants and/or by third parties in an effort to rebut a prima facie case made by the Office. According to Deputy Assistant Commissioner Kunin, the Office must regard as true any statements of fact made by applicants with respect to an asserted utility; if the Office does not regard the statement as true, the Office must provide evidence showing that one of ordinary skill in the art would not believe the statements to be true. Further, as Deputy Assistant Commissioner Kunin correctly stated, it would be improper to disregard any opinions made by a qualified expert in the particular field, whose opinion is based upon relevant facts, simply because the Office disagrees with the significance or meaning of the facts provided. (*See*, 82 JPTOS at 95 (2000); *see also* Revised Utility Examination Guidelines, *supra*, 40 Fed. Reg. 244 71442 (1999)). Indeed, if the Office rebuts the scientific opinion of a declarant, an applicant can request, and the Office must supply, an Examiner Declaration to support the rebuttal by the Office. (*See*, 37.C.F.R. §1.107 and MPEP §2144.03).

In the present case, and mindful of the Oeitker decision, Applicants respectfully submit that upon a full and fair review of this response, including the Declaration of Stanley J. Watson, M.D., Ph.D. a well known, highly credentialed, and highly regarded scientist who is familiar with this application, the claimed invention, the Office Action, and the drug discovery process, in considering the totality of this record, the Office will correctly conclude that based upon a preponderance of the

evidence, Applicants have more than met the "burden shift" such that the rejections of record must be withdrawn upon reconsideration, and the pending claims allowed.

## V. History Of Assignee

Arena Pharmaceuticals, Inc., assignee of the present claimed application, is a biotechnology based company which was incorporated in April of 1997 and completed an initial public offering in July of 2000 (Nasdaq:ARNA). During this period, Arena has increased in size from 4 co-founders to approximately 100 employees. Arena was established to exploit its proprietary technology for the direct identification of candidate compounds against constitutively active orphan receptors. Arena refers to this technology as "CART." Indeed, the Office will note that the filing date of the priority application in this case, April 14, 1997, is the date of incorporation for Arena.

Applicants assert that the utility of the claimed invention has received strong support from both the scientific and financial communities, and this support all but demands a conclusion that the claimed technology has a very real world use.

Based significantly upon the technology covered by the claims of this application, Arena secured both private and public financing during this brief three year period: between April 1997 and April 2000, Arena raised over $52 million in private financing; Arena's initial public offering raised over $124 million. The initial price for Arena stock was $18; since July 2000, the average trading price for Arena has been about $34.00 per share. Between January 2000 and April 2000, Arena entered into several collaborations based upon the technology covered by the present application:

In September of 1999, Arena announced a collaboration with Neurocrine Biosciences, Inc. Neurocrine has provided Arena with three (3) orphan GPCRs which Arena has and will constitutively activate by applying the technology as disclosed and claimed in the present case. This collaboration is on-going;

In January 2000, Arena announced a collaboration with Fujisawa Pharmaceutical Co., Ltd., a leading Japan-based pharmaceutical company with significant drug discovery research efforts. This collaboration also involves application of the technology covered by the pending claims to orphan GPCRs of interest to Fujisawa. During the collaboration, Arena will jointly validate up to thirteen (13) orphan GPCRs as drug screening targets. This collaboration is on-going;

In April of 2000, Arena announced a drug discovery alliance with Eli Lilly & Company, one of the world's leading pharmaceutical companies. Dr. August M. Watanable, Executive Vice President, Science and Technology, for Eli Lilly, stated in a press release issued in connection with the announcement of the collaboration that in reference to the technology covered by the claims pending in the application: "Arena has developed a very powerful platform for drug discovery that

could substantially speed up the overall process for drug development." Watanabe, A.M., M.D., Eli Lilly News Press Release, April 17, 2000, attached hereto as **Appendix A.** During this collaboration, both Arena and Eli Lilly will select a number of GPCRs for activation utilizing the claimed method. This collaboration is on-going;

On May 29, 2000 Arena entered into a collaboration with Taisho Pharmaceutical Co., Ltd. This collaboration involves application of the technology covered by the pending claims to orphan GPCRs of interest to Taisho. This collaboration is also on-going.

Applicants respectfully point out that those skilled in the art of discovering drug candidates, including well-known and well-established pharmaceutical organizations such as Eli Lilly, recognize the need for a technology that makes the drug discovery process more cost-effective and cost-efficient. As noted by Horn, F. and Vriend, G., "[a]ll pharmaceutical industries aim to design therapeutic drugs. Because the design of a new drug can cost up to 500 million dollars, anything that can make the process faster and cheaper is particularly welcome." Horn, F. et al., 76 Mol. Med. 464 (1998). Applicants respectfully point out that the claimed invention is such a technique that others have accepted as directed to accomplishing these objectives.

It is again noted: the claimed invention is focused on directly identifying candidate compounds having inverse agonist or agonist activity at constitutively activated G protein coupled receptors. In a recent article entitled, "Use of Constitutive G Protein-Coupled Receptor Activity for Drug Discovery," authored by scientists employed by one of the world's leading pharmaceutical companies, Glaxo Wellcome, Inc., Chen, G. et al. Mol. Pharm. 57:125-134 (2000), the following was stated,

> "The data presented with these [known] receptors indicate that a constitutive GPCR assay is a viable alternative for screening orphan receptors. The advantage of such an approach lies in the expanded window of detection. Not only will agonists be found but also inverse agonists. This option is not available in nonconstitutively active screens in which only positive agonists will be detected."
>
> ***
>
> "These data are consistent with the idea that constitutive GPCR systems can be made sufficiently sensitive and stable to be used for screening for ligands. The fact that all but one of the [known] receptors we tested provided substantial constitutive activity suggests that this approach would be especially useful for the screening of orphan receptors." Chen, G. et al. Mol. Pharm. 57:125-134, 131-132 (2000).

Applicants submit that the claimed invention is well recognized as providing a well established utility that is immediately apparent, or implied by the Specification's disclosure, alone or taken within the knowledge of one skilled in the art. Indeed, scientists from Glaxo Wellcome, who do not have a relationship with Arena (nor does Glaxo Wellcome), have stated after Applicants' priority date, that inverse agonists and agonists can be identified using constitutively active orphan GPCRs.

Indeed, on the basis of just the foregoing, Applicants assert that the claimed invention has met the requisite need of a specific and substantial utility and a well established utility.

With the foregoing in mind, Applicants address the specific points raised by the Office in the Action.

## VI. The Office Concedes and Admits That The Claims Provide a "Specific Utility"

The Office concedes and admits that claims 1-18, 33-34 and 39-40 provide a specific utility, *i.e.,* that it is the constitutively active form of receptors that can be used to directly identify lead compounds which affect receptor activity. The Office further concedes and admits that Applicants' claimed invention provides a means for discovering inverse agonists or agonists of the receptor without the need for the endogenous ligand.

## VII. The Office Presumably Concedes to Credibility of Asserted Utility

According to U.S. Patent and Trademark Office Training Materials For Revised Interim Utility Guidelines ("Guidelines"), Promulgated on March 7, 2000, a well established utility is a

> "specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." (*See*, page 7 of the Guidelines).

As noted above, a specific utility has been established. Applicants respectfully believe that the Office has conceded that the claimed invention provides a credible utility, *i.e.,* whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the reasoning provided." (*See*, page 5 of the Guidelines). The claimed invention is directed to a method of using constitutively activated orphan receptors to directly identifying candidate compounds (as inverse agonists or agonists) utilizing constitutively activated receptors. Because ligand-dependent activated receptors have been used for discovering modulators of the receptor function, then ligand-independent activated receptors (*i.e.*, constitutively activated receptors) can also be utilized, and has been utilized by Applicants, to discover compounds which act as inverse agonist or agonists of the receptor. Therefore, Applicants' asserted utility can not be questioned when all evidence and reasoning provided by the Specification is believable to a person of ordinary skill in the art. *See*, page 5 of the Guidelines.

## VIII. The Office Rejected Claims Under 35 U.S.C. §101 As Allegedly Not Providing A "Substantial Utility"

Claims 1-18, 33-34 and 39-40 have been rejected under 35 U.S.C. 101 allegedly because the claimed invention is not supported by either a specific ***and*** substantial asserted utility or a well established utility. According to the Office:

> A '**substantial utility**' is a utility that defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a '**real world**' context of use are not substantial utilities. A '**well established utility**' is a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A 'well established utility' must also be specific and substantial as well as credible."

The basis for the rejection (referred to herein as "Position A"), according to the Office is that the admitted specific utility is not substantial in the sense that the claimed invention does not define a real world use. The Office indicated that:

> Because an orphan receptor, does not have, by definition, a corresponding endogenous ligand that is known, **the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease states.**

In support of the rejection under Section 101(referred to herein as "Position B"), the Office notes the following:

> **Similarly, constitutively activated orphan receptors have no known function.**

Based upon these two positions, the Office asserts the following:

> Thus the corresponding asserted utilities are essentially methods of identifying lead compounds which affect constitutively activated orphan receptor activity, which does not define a "real world" context of use.

The Office then concludes with the following statement:

> "Since neither the specification nor the art of record disclose any activities or properties that would constitute a 'real world' context of use for the claimed method of identifying compounds having activity of inverse agonist or agonist activity, **further experimentation is necessary to attribute a utility to constitutively activated orphan receptors and to the compounds that bind the constitutively activated orphan receptors.**"

These positions are addressed below.

## A. Response to Office Position A

Position A: *Because an orphan receptor, does not have, by definition, a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease state.*

### 1. An Endogenous Ligand Is Not Required To Understand Receptor Function: Third Party Publications; Declaration of Stanley J. Watson, M.D., Ph.D.

Utilizing commercially available reagents, kits and protocols, an orphan receptor, *e.g.*, an orphan GPCR of interest to an artisan and selected by the artisan can be determined to be expressed in specific tissue within the body, including diseased or normal tissue. Upon determining the expression pattern of, *e.g.*, the GPCR, a person of ordinary skill in the art is credited with the ability to ascertain and assess the function of a receptor. Orphan receptors can be prioritized based upon the needs of the artisan desirous of exploiting this information, and one of ordinary skill in the art can utilize Applicant's claimed invention to directly identify candidate compound(s) that act as an inverse agonist to such receptor and/or agonist to such receptor. It is well known in the art that the expression pattern of a receptor provides the opportunity for one skilled in the art to develop information relevant to the normal function of the orphan receptor, and also for the opportunity to examine receptor distribution in tissues from disease states to assess clinical relevance. Those skilled in the art have stated,

> Tissue-specific expression of genes can provide clues to their role in pathology. Browne, M.J. 78 J. Biotechnology 247, 248 (2000).
>
> ****
>
> With the cloning of receptors, pharmaceutical research can follow a conceptual direction which is reverse to the traditional one...[S]ome advanced knowledge of the implications of the receptor-ligand system is desirable, but a significant place has to be left to the serendipitous discovery of therapeutic indications. The serendipity aspect of this endeavor may seem non-economical at first, but is bound to become increasingly accepted. After all, serendipity has been a large part of some resounding pharmaceutical success...[I]f novelty is the driving force in drug research, then entering the drug design at a stage when the biological system is not fully understood is a necessity. The ultimate reward of reverse pharmaceutical research is bound to be, in some cases, the marketing in drugs for large unmet medical needs. Civelli, O. et al 848 Brain Research 63, 64 (1999)

Attention is now drawn to the declaration of Stanley J. Watson, M.D., Ph.D. (hereinafter, "Watson Decla.") attached hereto as **Exhibit 1**.

Dr. Watson is a Professor & Research Scientist, in the Department of Psychiatry and Mental Health Research Institute, at the University of Michigan. At the University of Michigan, Dr. Watson also serves as the Associate Chair for Research, Department of Psychiatry. In 1970, Dr. Watson received his Ph.D. in Clinical Psychology from the University of Iowa, and in 1974 his M.D. from Tulane Medical School. Dr. Watson is licensed to practice medicine in the states of Louisiana, California, and Michigan. He is Board Certified in Psychiatry and Neurology. In addition, Dr. Watson has been on the Editorial Boards of several journals, including: Neuropsychopharmacology; Critical Reviews in Neurobiology; Molecular Neurobiology; and Peptide Research. Dr. Watson has been invited and has presented at over 100 scientific conferences and is an author and/or co-author of over 300 scientific papers. (*See*, Watson Decla. ¶1).

Dr. Waston has read the application, the Office Action issued by the Office and data presented herewith and has formed a scientific opinion, based upon his experience and the data provided to him, as to the utility of the claimed invention. Dr. Watson declares that he is familiar with the technology as set forth in the claims for direct identification of inverse agonists and agonists. (*See,* Watson Decla. ¶4). Based upon the totality of the information and his background, Dr. Watson disagrees with the conclusions reached by the Office that there is not a well established utility for the claimed invention. (*See,* Watson Decla. ¶5).

Dr. Watson opines that although having knowledge of a receptor's endogenous ligand is useful in defining the receptor function, such knowledge is not required to understand receptor function. Instead, in Dr. Watson's opinion, where a receptor is expressed; the systems and circuits within which a receptor is expressed in normal versus disease state; and changes in receptor expression in response to certain conditions that provide a plethora of information that can readily guide a scientist having routine skill to an understanding of the function of the receptor, without an absolute requirement of knowing the endogenous ligand for the receptor. (*See*, Watson Decla. ¶11). Simply stated, the function of an orphan can be understood before the endogenous ligand is identified, and the tools and skills necessary to secure this information are within the purview of the artisan who has selected an orphan receptor of interest to the artisan.

Those in the art previously understood that an advantage in identifying the endogenous ligand was to stabilize the receptor in its active state and search for compounds that interfere with the ligand for the binding site (*e.g.*, an antagonist). This simplistic and incorrect thinking prompted scientists to believe that one cannot identify, in the case of GPCRs, GPCR modulators without first having access to the GPCR's endogenous ligand. (*See*, Watson Decla. ¶15). It was not until relatively recently that the scientific community began to appreciate that the conformational states of GPCRs exists in equilibrium between a basal state (generally referred to as "R") and an active state

(generally referred to as "R*") where the receptor is able to function, and the receptor shifts from R to R*, and vice versa, in equilibrium. (*See*, Watson Decla. ¶17). In Dr. Watson's scientific opinion, the belief that receptor's exists in either an "on" and "off" position, whereby the endogenous ligand is required to turn the receptor "on" (*i.e.*, in the R* state), does not provide an adequate assessment of the GPCR function; rather, the location of a GPCR coupled with the respective cell types, circuits and organs strongly links that GPCR to its physiological function, and with a more modern-based understanding of the equilibrium states of GPCR function, provides a primary tool in understanding receptor function. (*See*, Watson Decla.¶22(a)(1)(a)).

Since the early 1990's, assays have been developed and kits manufactured to aid in the determination of a receptor's function. Such technologies include: homology data between receptors with an unknown and a known function; co-localization analysis with receptors with a known function; dot-blots; in situ analysis; northern analysis; and RT-PCR. These techniques have been utilized for nearly a decade and have become routine practice within the art for determining the distribution of the receptor and assessing their respective function.

Indeed, Applicants are not claiming receptor function. Applicants are not claiming receptors. Applicants are not claiming techniques for defining receptor function or in identifying orphan receptors. These are mere selection-based aspects, the tools for which are well within the scope of the claims. As with any method that may ultimately result in a pharmaceutical, rarely, if ever, is the first compound that is discovered the compound that is approved by the Food and Drug Administration (FDA). Indeed, it is through the routine and well known process of medicinal chemistry that selected criteria, *e.g.*, potency, stability, etc., are established. But, this being said, the compound that has defined attributes, *e.g.*, an inverse agonist to a selected orphan receptor, is a valuable material that itself has real world uses. Thus, by focusing on the function of orphan receptor, the Office creates a "straw-person" argument. This is not appropriate. The claimed method must be reviewed based upon what is claimed -- and since, as is established herein, understanding orphan receptor function is independent of the claimed method and a matter of the selection by an artisan, the following merely provides a brief overview of how readily the skilled artisan can ascertain the function of a selected orphan receptor.

### 2. Techniques Used to Ascertain Receptor Function

With due respect, the Office has rejected claims 1-18, 33-34 and 39-40 based upon a traditional dogmatic approach that is not related to the claimed invention. This traditional approach relies upon finding the endogenous ligand prior to searching for receptor modulators (generally antagonists), while the claimed invention relies on a constitutively activated orphan receptor to

directly identify candidate compounds (inverse agonists or agonists) without the need for the receptor's endogenous ligand.

According to Dr. Watson, inverse agonist and agonists are classes of compounds that by definition must affect the function of the receptor, *e.g.*, the receptor's signaling consequences and response to activation and/or inhibition of function. (*See,* Watson Decla. ¶22(a)(1)(a)). These compounds, by definition, do not simply bind to a receptor but rather affect the function of the receptor.

Indeed, based upon the evidence provided herein, the Office is incorrect in stating that because an orphan receptor, by definition, does not have an endogenous ligand that is known, that the function of an orphan receptor cannot be determined. As Dr. Watson makes clear in his declaration, in his opinion the function of orphan receptors can be ascertained and assessed using routine procedures within the purview of a person of ordinary skill in the art, *e.g.*, through homology data, or traditional tissue distribution methods, for example, Reverse Transcription-PCR ("RT-PCR"), dot-blots, northern-blots, co-localiztation analysis and in situ hybridization. Determining the tissue distribution of a receptor can be accomplished by purchasing commercially available kits and following manufacturer's instructions. Table A below lists several examples of routine techniques and commercially available kits, used to determine the tissue distribution of a receptor and the manufacturer of the kit, reagents and protocols utilized to accomplish these routine techniques.

**TABLE A**

| **Technique** | **Manufacturer/Protocol** |
|---|---|
| RT-PCR | Clontech |
| Dot-Blot | Clontech |
| Northern Analysis<br>▪ RNA isolation from cells<br>▪ Synthesis of probe<br>▪ Hybridization | <br>▪ Gibco/BRL<br>▪ Stratagene<br>▪ Clontech |
| In situ Hybridization<br>▪ rTth DNA Polymerase<br>▪ Autoradiography<br>▪ Male Sprague-Dawley Rats | <br>▪ Perkin Elmer<br>▪ Kodak XAR-5 film<br>▪ Charles River |
| Co-localization | Protocol set forth in Marks, D.L. et al, 3 *Mol. & Cell. Neuro.* 395 (1992) |
| Homology Analysis | DNA STAR™ |

In Dr. Watson's opinion, it is the routine techniques by which a skilled artisan utilizes to determine the location of a receptor within the body. (*See,* Watson Decla. ¶22(a)(1)(a)). Not only does Dr. Watson assert that determining the location of a receptor helps in the understanding receptor function, but others knowledgeable in the field of functional genomics have agreed with this position: "the expression pattern can determine whether a receptor is expressed in a normal or diseased tissue of interest as a therapeutic target," and that a "highly selective tissue expression profile can also provide a clue to receptor function." (*See,* Browne, M.J, 78 *Biotechnology* 247, 248 (2000)).

As is apparent, those in the art of drug discovery understand that ascertaining the function of a receptor simply requires the use of routine skill and technique together with commercially available products. Endogenous ligand alone is neither dispositive nor required. And with due respect and mindful of 37 C.F.R. §1.107 and MPEP §2144.03, the Office has not supported its view with anything other than the opinion of the Office. In this context, Oetiker requires withdrawal of the rejection based upon the Watson Declaration.

### 3. Application of Commercially Available Techniques with Orphan GPCRs to Deduce Receptor Function

Following routine techniques disclosed in the manufacturer's instructions of commercially available kits, a person skilled in the art is credited with the ability to determine a receptor's tissue distribution, whether the receptor is expressed in diseased or normal tissue cells, if the receptor target is homologous to other known receptors or, based upon the distribution, the functional role of a receptor.

The function of a receptor is not determined, as the Office incorrectly stated, by first identifying the endogenous ligand. In the early development of understanding receptor function, the ligand was thought to be required to identify modulators which act on the receptor of interest. In Dr. Watson's opinion, knowing a priori, the endogenous ligand is not required in understanding the function of an orphan GPCR, because a skill artisan can appreciate a functional role before the endogenous ligand is identified. (*See,* Watson Decla. ¶22(a)(1)(a)). It is again noted: on the basis of Dr. Watson's Declaration alone, in the absence of evidence proffered by the Office in support of its position, that the rejection under Section 101 must be withdrawn upon reconsideration.

The following are examples of utilizing routine techniques and commercially available reagents, procedures and kits to aid in understanding and determining receptor function. It is noted that none of the following orphan GPCRs are the subject of any of the collaborations noted above.

Those collaborations involve different GPCRs, the majority of which being orphan GPCRs that were provided to Arena by the third party.

Applicants note that for confidentiality reasons, Arena has used Arena code names when referring to the orphan GPCRs and chemical compounds directly identified using the claimed invention discussed above. **Appendix H** is a table indicating the receptor code name and the respective receptor public name. The disclosure of the public names and structures are believed not to be material to the patentability of the claimed invention. According to MPEP § 724.02, any information which is considered by the party submitting the same to be trade secret or proprietary material can be submitted in a sealed enveloped and clearly labeled as "Trade Secret" or "Proprietary" document. However, together with this Response Applicants have provided for the Office's convenience an **Appendix H** in redacted form.

**(a) Receptor Function: Regulation of Insulin Secretion**

Utilizing routine techniques and commercially available procedures, kits and reagents, an orphan receptor 19AJ was determined to be naturally constitutively active. A whole-cell cAMP assay comparing the endogenous 19AJ with a control (pCMV) was utilized. (*See*, cAMP Assay Protocol, **Appendix B1** and **Appendix B2** for the graphic results). **Appendix B2** evidences that 19AJ produces about a 20 fold increase in cAMP compared to the control.

Again, utilizing a commercially available human tissue dot-blot format (Clontech), the endogenous 19AJ receptor was used to probe for a determination of the areas where 19AJ is localized. (*See*, Dot-Blot Protocol, **Appendix B3**). According to the results, 19AJ is abundantly expressed in the pancreas (D3) and fetal liver (G4). (*See*, **Appendix B4**). On these basis of this information, 19AJ was considered to have a role in pancreatic functions, such as insulin production.

To confirm the results obtained from the RNA dot-blot, a reverse-transciptase PCR technique ("RT-PCR") was utilized. RT-PCR was performed using 19AJ specific primers and human multiple tissue cDNA panels (Clontech) as templates. Taq DNA polyermase (Stratagene) was then utilized for the PCR reaction. (*See*, RT-PCR Protocol, **Appendix B5**). The 16 human tissues in the cDNA panel utilized (brain, colon, hart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus, leukocyte, and liver) evidenced a single 19AJ band only from the pancreas (panel G). (*See*, **Appendix B6**).

With the knowledge that the pancreas plays a major role in the production of insulin, a northern blot analysis was further utilized with RNA from several exocrine and endocrine pancreatic cell lines and determined that 19AJ receptor was expressed in several insulin-derived glucose-responsive cells. (*See*, Northern Analysis Protocol, **Appendix B7** and **Appendix B8** for the results).

These data indicate that even without knowing the endogenous ligand to the 19AJ receptor, one of ordinary skill in the art using routine skilled techniques can understand and assess the functional role of 19AJ, *i.e.*, 19AJ is involved in insulin secretion. (*See*, Watson Decla. ¶19).

Based upon the determination that (a) 19AJ is naturally constitutively active, (b) 19AJ is specifically expressed in the pancreas, and more specifically in the beta cells in the islets of the pancreas and (c) the cells expressing 19AJ are insulin producing, glucose-responsive which substantially increased insulin secretion, this orphan receptor was selected for direct identification of candidate compounds that would exploit this information, *i.e.*, an agonist. Accordingly, the claimed invention was applied to 19AJ and this method led to the direct identification of a candidate compound, Cmd A, according to the protocol disclosed in the Specification. To confirm that Cmd A functions to stimulate the production of insulin, a routine technique was utilized, together with commercially available procedures, kits and reagents, to determine that Cmd A increases the insulin production in the presence of glucose when compared to the basal level of 19AJ. (*See*, Insulin Assay Protocol, **Appendix B9** and **Appendix B10** for the results). Appendix B10 compares glucose-responsive insulin secreting cell line ("Tu6") and Tu6 transfected with 19AJ ("Tu6/19AJ"), both in the presence of Cmd A. Comparing Tu6/19AJ in the presence and in the absence of Cmd A, cells transfected with 19AJ in the presence of Cmd A evidence about a two (2) fold increase in insulin production. (*See also*, Watson Decla. ¶22(a)(2)(a)).

Based upon the foregoing, and in accordance with the claimed invention an agonist of a constitutively activated 19AJ receptor was directly identified even without knowing the endogenous ligand for 19AJ. This small molecule thus provides the basis for development of small molecule therapeutics for the treatment of, *e.g.*, diabetes.

**(b) Receptor Function: Regulation of Feeding**

The orphan GPCR 18F was determined to evidence natural constitutive activation. Utilizing a reporter assay, a routine technique, together with commercially available procedures, protocols kits and reagents, the relative light units generated upon receptor expression were measured. (*See*, CRE-Luc Reporter Assay Protocol, **Appendix C1** and **Appendix C2** for graphic results). Utilizing in situ hybridization, a routine technique, tissue samples were examined for expression of orphan receptor 18F. (*See*, In situ Hybridization Protocol, **Appendix C3**). It was determined that the 18F receptor is expressed in the following areas of the brain: hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex. 18F receptor is presented in the dark areas in **Appendix C4**; **Appendix C5** provides a reference map of the rat brain. Based upon the localization pattern, a relationship between the 18F receptor and metabolism and/or feeding behavior was surmised.

In situ hybridization analysis, according to the protocol of **Appendix C3**, was conducted using routine techniques on both lean and obese male Zucker rats. As those in the art appreciate, Zucker rats are genetically bred to result in animals that exhibited a lean or obese phenotype. **Appendix C5** provides a representative tissue section of 18F receptor expression in the lean Zucker animals; **Appendix C6** provides a representative tissue section of 18F receptor expression in the obese Zucker animals; and **Appendix C7** is a reference map of this section of the rat brain.

Based upon these data, and based upon the opinion of Dr. Watson, the distribution of 18F in the hypothalamus indicates involvement in feeding behavior. Therefore, the function of the 18F receptor in obesity was indicated by these data. (*See also*, Watson Decla. ¶22(a)(2)(b)).

In further evaluating the 18F receptor as a target receptor of interest, the protocol described in Marks, D.L. et al., 3 Mol. & Cell. Neuro. 395 (1992) was utilized to functionally assess the co-localization of 18F with that of the neuropeptide agouti-related peptide (AGRP), which is known to be related to feeding behavior. AGRP was analyzed in conjunction with radiolabeled 18F and both were found to be co-localized in the arcuate (*see* **Appendix C9**). **Appendix C9** provides results from a co-localization experiment, evidencing that 18F and AGRP are co-localized within the arcuate. The arrow directs attention to a specific cell within the arcuate, with the circle surrounding the cell; the "dots" are radiolableled 18F, and beneath those, in a darker shade, is AGRP. Given the role that AGRP plays with respect to homeostasis, and further given that 18F is constitutively active in its endogenous state, the results obtained would be consistent with these data in that the almost immediate, significant loss of weight can be understood in the context of 18F influencing AGRP.

In determining that the 18F receptor was a receptor target of interest, the claimed invention was applied to directly identify a candidate compound, ARE112[1]. **Appendix C10**, attached hereto, is a primary plate profile evidencing inverse agonist activity of directly identified compound ARE112 to 18F receptor, utilizing the claimed methods. As a candidate lead compound, ARE112 evidenced a decrease in food intake after intracerebroventricular (ICV) and oral (PO) administration. The in vivo protocols are attached hereto as **Appendix C11** and the results are presented in **Appendix C12**[2]. These data indicate that the orphan GPCR 18F is an orphan receptor target for use in the discovery of compounds that could be useful in the treatment of obesity. These data illustrate the utility of the claimed invention in rapidly identifying small molecule regulators of therapeutically-relevant GPCRs.

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[1] ARE112 is a compound directly identified in accordance with the claimed invention; no position is taken as to whether or not this may be the actual compound used for the potential treatment of *e.g.*, obesity.

[2] ARE112 is a compound which is disclosed and claimed in a co-pending and commonly assigned patent document PCT Application Number PCT/US00/04945.

The location of 18F receptor makes available to the skilled artisan the receptor's functional role. Upon utilizing routine techniques, it is possible to understand the internal mechanism of a receptor of interest to directly identify compounds that modulate the receptor that are potentially useful in the treatment of disorders such as obesity. Application of the claimed invention has led to the direct identification of the compound ARE112 that is an inverse agonist of 18F receptor. ARE112 was then administered to animals to determine the in vivo effects of the compound. As is apparent in **Appendix C12**, the treated animals decreased food consumption, increased fat metabolism and lost weight. Therefore, the data presented in this example strongly demonstrates that the conclusion made by the Office, *i.e.,* that the claimed invention has no real world use, is unsupportable. (*See also*, Watson Decla. ¶22(a)(2)(b)).

**(c) Receptor Function: Regulation of Cell Growth**

Utilizing a northern blot analysis technique, a routine protocol, together with commercially available procedures, kits and reagents, three orphan GPCRs have been demonstrated to be up-regulated in tumor cell and cell lines. (*See*, Northern Blot Analysis Protocol, **Appendix D1**.

The results of RNA blots evidence that the orphan receptor 19Y was abundantly expressed in tumor uterus tissue ("T") when compared to the normal uterus ("N") cells, where no expression of 19Y was detected. (*See*, **Appendix D2**). Utilizing routine techniques, these data indicate that 19Y plays a role in the regulation of uterine carcinogenesis. Results of RNA blots for a second orphan GPCR, 18A, evidence that the 18A receptor is overexpressed in ovarian tumor tissue when compared to normal ovarian tissue. (*See*, **Appendix D3**, panel 1). In addition, expression of 18A was also detected in the tumor cells of three breast tissues as compared to normal breast tissues. (*See*, **Appendix D3**, panel 2). Again, utilizing the routinely applied technique of northern analysis, and assessing the expression pattern of 18A, the function of 18A was deduced, *i.e.,* 18A plays a role in regulating the proliferation of cells in the ovaries and breasts. The third orphan GPCR is referred to as 18AI. The RNA blots for the 18AI receptor evidenced an abundant expression in colorectal cancer cell lines (*e.g.,* SW480), indicating that 18AI plays a role in the colorectal carcinogenesis. (*See*, **Appendix D4**).

In these three examples, utilizing routine research techniques and skills well within the realm of scientists in this area, the expression patterns indicate that the receptors (*i.e.*, the mRNA) are up regulated in tumor cancer cells, and this associates the receptors with their respective pathological conditions, all in the absence of <u>any</u> discernable understanding of the corresponding endogenous ligands for these receptors. This substantial up-regulation is an apparent response to a defined condition, such as tumorgenesis. Accordingly, these examples point toward a function for an orphan

receptor which can be determined without knowing the endogenous ligand, because of the differential expression patterns in normal tissue versus abnormal or diseased tissue. (*See*, Watson Decla. ¶22(a)(2)(c)).

After evaluating and selecting 19Y as a receptor target of interest for the regulation of tumorgenesis, the claimed invention was used with 19Y to directly identify two candidate compounds, Cmpd 1 and Cmpd 2. With the knowledge that 19Y is abundantly expressed in tumor cells, a routine proliferation assay technique was used (Roche Molecular Biochemicals, Cat. No. 1644807) as a method for quantifying cell proliferation. (*See*, Proliferation Assay Protocol, **Appendix D5**). In this assay, 19Y was transfected into prostate cancer cells (PC-3) and was measured in the presence and absence of the candidate compounds. (*See*, **Appendix D6**). According to the data of **Appendix D6**, 19Y, in the absence of any compound, evidence an induction of PC-3 cell proliferation when compared to the control ("CMV"). (*See*, red bar of Appendix D6). With the addition of the candidate compound, a decrease in cell growth was observed, as measured by the decrease in optical density when compared to the 19Y in the absence of compound. Thus, according to the definition of an inverses agonist, *i.e.*, a compound that inhibits the functional activity of a receptor, Cmpd 1 and Cmpd 2 are considered to be inverse agonists against the 19Y receptor. (*See,* yellow and blue bars of Appendix D6). These compounds, then, provide the ability to develop unique therapeutic candidates for the potential treatment of, *e.g.*, uterine cancer.

Utilizing routine skill and commercially available reagents and kits, 19Y was determined to be abundantly expressed in tumor cells of the uterus but not in the normal cells. Upon application of the claimed invention, two candidate compounds were identified and determined to inhibit the proliferation of prostate cancer cells. Stated again, based upon the expression pattern of 19Y, this receptor was determined to play a significant role in cancerous conditions. For that reason, the claimed method has allowed for the advancement of a unique approach to the understanding and possible treatment of uterine cancer. Based upon the examples presented in this section, the claimed method provides for an irrefutable real world use of the claimed invention. (*See*, Watson Decla. ¶22(a)(2)(c)).

**(d) Receptor Function: Regulation of Ischemic Damage**

Another commercially available technique for assessing receptor function was accomplished by utilizing data collected from homology analysis. This routine procedure was utilized with respect to an orphan GPCR 19BX by initially conducting a BLAST™ search, whereby the receptor protein of interest is used as a query in search for other similar or homologous sequences provided in the publicly available database, GenBank. Upon such a search, 19BX was determined to be homologous

to a chemoattractant receptor, referred to as complement 5a receptor (C5a-R). Utilizing a commercially available software, DNA STAR™, 19BX was determined to be about 30% homologous to C5a-R. (*See*, **Appendix E1**). C5a-R is a chemoattractant receptor which has been reported to be involved in inflammation.

In further evaluating 19BX as a receptor target of interest, a commercially available dot-blot kit (Clontech) was utilized to determine the receptor's expression pattern. The dot-blot evidenced that 19BX is expressed mainly in the brain, as indicated in columns 1 and 2 of **Appendix E2**. **Appendix E3** is a grid indicating the various tissues and their respective locations. Because 19BX receptor was specifically expressed in the brain, an in situ hybridization technique was utilized to evaluate 19BX in the brain. (*See*, In situ Hybridization Assay Protocol, **Appendix E4**). As outlined in **Appendix E5**, the arteries found in the brain of the rat were momentarily closed for one (1) hour, causing blood-flow to stop, thus leading to a buildup of blood pressure, also known as MCA occlusion. The arteries were then restored of their blood flow for various amounts of time, also referred to as reperfusion, and then analyzed for an up-regulation of 19BX. According to **Appendix E5**, an abundant expression of 19BX was evidenced specifically in the ipsilateral cingulated cortex, in a time dependent manner. (*See,* panels 1-9 of **Appendix E5**). In northern blot assay, 19BX was determined to be expressed on the neurons of the hippocampus. (*See*, **Appendix E6**).

In an effort to delineate the G protein coupling of 19BX, routine skills were utilized together with commercially available kits to determine that 19BX is a Gq linked receptor. (*See*, AP1-Luc Reporter Assay Protocol, **Appendix E7**). **Appendix E8** indicates that both endogenous 19BX ("19BX wt") and a non-endogenous, constitutively activated version of 19BX couples to the Gq protein as evidenced in the increased luciferase signal when compared with the control ("CMV"). A receptor that couples to the Gq protein is mediated by calcium [$Ca^{2+}$]. The fact that 19BX signals via the Gq protein is indicative of readily understanding a protein (Gq) modulated by a constitutively activated orphan receptor (19BX). But this knowledge provides substantially more insight into the functional role of 19BX.

To summarize the functional role of 19BX, based upon the data presented herewith, it has been determined that when the brain is shocked or suffers from physical pain (*e.g.*, via MCA occlusion), 19BX is up-regulated. This up-regulation stimulates the coupling of Gq to 19BX, which then causes an influx of calcium into the cells. A surplus of calcium in the cell will eventually lead to the death of the cell. Therefore, based upon the data which evidence that: 19BX is up-regulated in response to an ischemic condition; 19BX is expressed in the brain, specifically in the neurons of the hippocampus; 19BX is Gq coupled, it was readily, a deduction to which Dr. Watson has agreed, that the functional role of receptor is involved in neuronal survival. (*See*, Watson Decla. ¶22(a)(2)(d)).

**(e) Receptor Function: Regulation of Injured Nerve Cells**

Utilizing routine techniques and skill together with commercially available procedures, kits and reagents, orphan receptor 19M was determined to be expressed in Schwann cells. (*See,* Northern Analysis Protocol, **Appendix F1**). **Appendix F2** is a northern blot indicating that addition of forskolin at 20μM evidence that myelination was maintained. Schwann cell are significant in the sense that they act to repair injured nerves (also referred to as axons) by forming myelin sheaths around them. The greater the amount of myelin sheaths around the axons, the faster action potentials travel, thus allowing one's body to conserve more metabolic energy.

In another northern analysis assay according to that disclosed in **Appendix F1**, 19M was determined to be over-expressed in crushed rat sciatic nerves, specifically seven (7) days after crushing the nerves. (*See*, **Appendix F3**). Such data is consistent with the data presented in **Appendix F2**, *i.e.,* 19M evidences a role in the regeneration of nerves by stimulating the process of myelination in Schwann cells.

By utilizing routine skill and commercially available products, a functional role for 19M was deduced even without knowing the endogenous ligand. Upon selection of this receptor, followed by application of the claimed invention, an inverse agonist against 19M is preferred in diseases or disorders that are involved in hyper-myelination (*e.g.*, tumorgenesis), while an agonist is preferred in disease or disorders involved in hypo-myelination (*e.g.*, diabetes). (*See*, Watson Decla. ¶22(a)(2)(e)).

**(f) Summary**

The functional role of an orphan receptor can be assessed and understood prior to identifying a receptor's endogenous ligand. As opined by Dr. Watson: where a receptor is expressed; the systems and circuits within which a receptor is located; how the receptor is expressed in normal versus disease state; and changes in receptor expression in response to certain conditions all provide the type of information that can readily guide the skilled artisan to deduce the functional role of a receptor. Simply stated, drug discovery does not require the identification of a receptor's endogenous ligand. Today, established pharmaceutical organizations such as Eli Lilly and Glaxo Wellcome recognize the need for faster and more cost-effective methods of finding modulators of receptors without having to spend several years and millions of dollars in search for the endogenous ligand.

Although knowing the endogenous ligand may be useful in understanding receptor function, as has been established herein, access to the endogenous ligand is not required to understand receptor

function. The assignee of the application has provided numerous examples whereby the functional role of a receptor has been deduced by utilizing routine skill and techniques together with commercially available procedures, kits and reagents. Applicants respectfully note that these techniques are performed prior to applying the claimed invention as a means of assisting one skilled in the art to select a receptor target of interest. Selection of an orphan receptor is just that -- a matter of selection. Such selection is within the discretion of the artisan.

When the artisan has deduced a functional role for an orphan receptor and has selected that orphan receptor, the claimed invention provides a real world use by which candidate compound(s) can be directly identified against constitutively activated orphan receptors. Stated again, by utilizing routine techniques, one skilled in the art is able to assess and understand the functional role of a receptor. Upon determining the role, the claimed invention can be applied to the receptor target whereby an inverse agonist or agonist can be directly identified. This is a real world use for the claimed invention. That the skilled artisan may decide to conduct additional studies using such compounds (*e.g.,* medicinal chemistry to ascertain if more potent, cost-effective drugs can be developed) is not dispositive -- this is a function of all drug development. Rarely, if ever is a lead compound the drug that is marketed. A lead is just that -- a lead. This is a nuance of drug discovery; the Guidelines can make no judgment on this aspect of drug discovery because if this were the case, the Guidelines would prohibit securing a patent on anything other than those drugs proven to be safe and effective and approved for commercialization by the FDA.

Applicants respectfully point out that by definition, an inverse agonist and an agonist are compounds that upon binding to the receptor target, modulate the function of a receptor compared to the receptor's natural functional activity. Stated differently, an inverse agonist of a constitutively activated receptor acts to shift the equilibrium of the receptor to an inactive state, thereby inhibiting the natural functional activity of the receptor. Conversely, an agonist of a constitutively activated receptor shifts the equilibrium of the receptor to the active state, thus activating the functional activity of the receptor. These two classes of compounds of a constitutively activated receptor can be directly identified because they impact the receptor's normal downstream signaling system. Because these downstream systems are based upon G proteins, one skilled in the art can understand the proteins modulated by an orphan GPCR. (*See,* Watson Decla. ¶18).

In addition to serving as lead drug candidates for drug discovery purposes, a significant and useful aspect of the claimed invention is that the discovery of inverse agonists and agonists provide for a better understanding of the cellular signaling response elements of a receptor. (*See*, Waston Decla. ¶18).

Based upon the data presented, Dr. Watson declares that the claimed invention provides for a well established utility because, *e.g.*, drug discovery can be conducted with orphan GPCRs even when the endogenous ligand has not yet been identified. Further, in his opinion, the candidate compounds identified by the claimed method are within a class of compounds that, by definition, act to change the function of a receptor's endogenous functional activity. Thus, they do far more than merely "bind" to the receptor. In Dr. Watson's opinion, because GPCRs are coupled to G protein, any compounds identified will act to modulate these proteins, affecting the downstream functional activity of a receptor.

In view of the foregoing, Applicants submit that the basis of the rejection under Section 101 predicated upon Position A cannot be sustained. Under a preponderance of evidence, it is Applicants' position that they have more than met the burden shift. Therefore, Applicants respectfully request that the rejection under Section 101 be withdrawn upon reconsideration.

**B. Response to Office Position B**

Position B: *Similarly, constitutively activated orphan receptors have no known function.*

G protein coupled receptors (GPCRs) are known to exist in equilibrium. GPCRs shift from an inactive state (R) to an active state (R*) and vice versa. The active state is typically stabilized by an endogenous ligand. This active state allows for the receptor to bind to its endogenous G protein where upon coupling of the G protein, several cascade of events may occur, *e.g.*, bound GDP is converted to GTP; and depending on which G protein couples to the receptor, adenylyl cyclase is stimulated or inhibited resulting in an increase or decrease, respectively, of cAMP; or an increase or decrease of inositol triphosphate.

In the mammalian body, constitutively activated receptors have been known in the art to play an important role in disease function. These natuarlly constitutively activated receptor versions shift the equilibrium to the activated state and remains in the active or "on" position without the need for the endogenous ligand, *i.e.*, GPCRs that are activated through a ligand-independent fashion are considered to be constitutively active receptors. These naturally active receptors may or may not be mutated, but have the same effect as a non-endogenous, constitutively activated GPCR, such that these receptors are stabilized in the "on" position, thereby causing the receptor to continuously stimulate the production of, for example, cAMP.

Naturally occurring constitutively active receptors, for example, thyrotropin receptor, lutenizing hormone receptor, rhodopsin receptor, V2 vasopressin receptor and adrenocorticortropic

hormone receptor, have all been determined to consist of different versions containing deletions or alterations in the receptor sequence, which may cause receptor dysfunction. In these instances, the dysfunction can lead to an interference with the functioning of organs or systems that can be lethal, *i.e.*, gain of function or a loss of function. For example, a gain of function caused by a mutation in the GHRH receptor results in constitutive activation of the adenylyl cyclase. As the cAMP cascade is stimulated, growth hormone (GH) production is increased due to the overproduction of cAMP, resulting in clonal hyperfunctional tumor. (*See*, Parma J. et al., 100 *Mol and Cell Endocrin*159 (1994)).

Table B below lists several naturally active receptors and the hereditary condition caused by the constitutively active receptor.

**TABLE B**

| Receptor Name | Hereditary Condition |
|---|---|
| Thyrotropin receptor | Hyperthyroidism |
| Parathyroid hormone receptor | Parathyroidism |
| Lutenizing hormone receptor | Precocious puberty |
| Rhodopsin receptor | Retinitis pigmentosa |
| V2 vasopressin receptor | X-linked nephrogenic diabetes insipidus |

The traditional approach to turning "off" a receptor is to search for an antagonist which would compete for the endogenous ligand. However, because constitutively active receptors are agonist-independent, an antagonist would be a compound whose binding does not alter the position of the equilibrium between the active state and the inactive state because there is no agonist to compete with. (*See*, Watson Decla. ¶17). Inverse agonists are compounds that preferentially stabilize the inactive conformation of a GPCR. As a result, inverse agonists to GPCRs display a decrease in intrinsic ability of a receptor to activate the cellular G protein coupling, and thus decrease the functional activity of the receptor. (*See*, Watson Decla. ¶17).

As illustrated above, 19AJ is an example of an endogenous, constitutively active receptor. (*See*, Appendix B2). However, this receptor does not contain a deletion or mutation which causes a disease or dysfunction. Instead, 19AJ has been determined to be specifically expressed in the islets of the beta cells in the pancreas, where upon glucose stimulation, insulin is secreted. Another example of an endogenous, constitutively active receptor is 18F, as illustrated above. (*See*, Appendix C2). Based upon the up-regulation of 18F in the hypothalamus, 18F was deduced to be involved in feeding behavior and upon direct identification of an inverse agonist to 18F, and subsequent in vivo

evaluation, this deduction was confirmed. Similar to 19AJ, 18F receptor does not contain mutations or deletions, but is endogenously, constitutively active.

According to the numerous examples of the endogenous, constitutively active receptors, listed and discussed above, Applicants respectfully disagree with Position B taken by the Office. It has been shown that several constitutively active receptors, including altered and unaltered receptors, are found in the human body. Further, it has been reported that these constitutively active receptors that are naturally altered or mutated are capable of causing diseases. The mere existence of naturally active receptors in the body indicates that 19AJ and 18F are biologically functionally active. (*See,* Waston Decla.¶22(b)(1)).

Applicants respectfully submit that these two examples, and other constitutively active receptors, have a biological functional purpose that is of substantial use; otherwise such receptors would not exist in the body. Therefore, because endogenous, constitutively active receptors have a substantial utility, the claimed method also must have a substantial utility – it is the constitutively activated receptors that are utilized to identify candidate compounds that bind to the receptors.

Indeed, in Dr. Watson's opinion, it is both scientifically and factually incorrect to assert that constitutively activated orphan receptors have no known function. (*See,* Waston Decla.¶22(b)(1)). Again, in the absence of evidence to the contrary, the opinion alone requires a withdrawal of the rejection upon reconsideration.

In view of the foregoing, Applicants submit that the basis of the rejection under Section 101 predicated upon Position B cannot be sustained. Accordingly, Applicants respectfully request that the rejection under Section 101 be withdrawn upon reconsideration.

According to the revised Utility Guidelines, and the reasonings and arguments submitted herewith, Applicants have clearly met the burden shift of providing evidence to establish that the claimed invention provides a specific (as conceded by the Office) *and* substantial utility. In addition, Applicants have proffered evidence in the Specification and in this Response that proves an immediately apparent well established utility. Therefore, the view of Oetiker and the points cogently expressed by Deputy Assistant Commissioner Kunin, Applicants respectfully submit that the rejection under Section 101 must be withdrawn upon reconsideration.

### a. Claims Rejected Under 35 U.S.C. §112, First Paragraph

Claims 1-18, 33-34 and 39-40 were rejected under 35 U.S.C. §112, first paragraph because the claimed invention is allegedly "not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

With due respect, because claims 1-18, 33-34 and 39-40 were rejected under 35 U.S.C. §112, first paragraph solely because the claimed invention did not allegedly provide for a well established utility nor a substantial utility, *and* because Applicants have established a well established utility and a substantial utility that would constitute a real world use, one skilled in the art would clearly know how to use the claimed invention. Therefore, Applicants respectfully request that this rejection also be withdrawn upon reconsideration.

## IX. Brennar v. Manson Supports Applicant's Position

The Guidelines, and the Office Action, have placed reliance on Brennar v. Manson, 383 U.S. 519, 148 USPQ 689 (1966) as a basis for explaining the concept behind the phrase "real world" use for a claimed invention to comport with 35 USC 101. As with the Guidelines, the Office makes reference to the view asserted by the Supreme Court in Manson:

> Congress intended that no patent be granted on a chemical compound whose "utility" consists of its potential role as an object of use testing[.] [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

This well-settled, and oft-quoted, proposition is not disputed by Applicants. However, this quote, as used by the Office to support its conclusion of no "real world" use of the claimed invention, requires context. In a properly construed context, Applicants assert that Manson supports Applicants' position.

With due respect, the citation to Manson highlights the problems that can arise when a statement by a court is thrust naked into a legal discussion, without the benefit of the facts of the case which provide the required context.

Manson was taken upon writ of certiorari from a CCPA decision that reversed a Board of Appeals decision holding that Manson had established utility under Section 101 for a claimed chemical process. Manson had attempted to provoke an interference proceeding with claims of a 1959 patent (2,908,693; attached hereto as **Appendix G**) having a claimed priority date of December 17, 1956. Manson, whose application was filed in January 1960, claimed that he had invented the process of the '693 patent prior to December 17, 1956.

The '693 patent issued with four process claims for production of 2-methyl-dihydrotesterones. Six examples were provided therein, all being directed towards production of such products. A single statement regarding the use of such products was provided in the specification:

> The products of the process of the present invention have a useful high anabolic-andriogenic ratio and are especially valuable for the treatment of those ailments where an anabolic or antiestrogenic effect together with a lesser androgenic effect is desired. Col. 1, lines 21-26.

Manson's application claimed the same process as the '693 patent. However, and proving to be a crucial fact, Manson disclosed no utility for the compound made by the process. Indeed, upon original rejection of the claims by the examiner under Section 101, Manson attempted to support utility by reliance upon a 1956 article. The article did not focus on the compound disclosed by Manson in his application; as noted by the Manson Court, the article cited by Manson:

> revealed the steroids of a class which includes the compound in question were undergoing screening for possible tumor-inhibiting effects in mice, and that a homologue adjacent to Manson's steroid had proven effective in that role. Emphasis supplied. 148 USPQ 690.

Manson provided absolutely no indication of any utility for the product made by the claimed process and, indeed, even his cited reference did not focus on the compound made by the Manson process, but rather a class that included the compound that, according to the reference, may prove to be useful in the role recited in the reference. Thus, without any utility for the compound provided by Manson in his original application, the Court agreed with the decision of the Board, and reversed the holding of the CCPA.

*On these facts*, the statements made by the Supreme Court are clear, and indeed, the Guidelines, *when properly applied*, would presumably lead to the same result reached by the original examiner who reviewed Manson's application, *i.e.*, with absolutely no disclosure of any utility for a product made by a claimed process, there can be no utility for that process under Section 101.

However, when the Supreme Court's oft-cited quote is taken out of context, it is not difficult to understand that Manson can be used to support a variety of even conflicting positions. But Manson merely underscores the original Congressional intent behind the 1952 Patent Act regarding Section 101 – an applicant must disclose some identifiable benefit for the claimed invention in order to be patentable under Section 101.

A recent decision from the Court of Appeals for the Federal Circuit is helpful in this context. In Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999) (attached hereto as **Appendix I**), the claimed invention was directed to a "post-mix" beverage dispenser. Unlike a "pre-mix" dispenser that mixes the ingredients of a beverage prior to dispersion for customers, the claimed post-mix dispenser separates the ingredients which are not mixed until the beverage is dispensed; however, and simply for marketing purposes, which purposes proved to be

the lynch-pin for the asserted utility, the claimed post-mix dispenser was designed to look like a pre-mix dispenser, *i.e.*, a visible reservoir contained a fluid that looked like the beverage, and the reservoir looked like the source of the beverage being dispensed to customers, even though it was not.

In an action for infringement, summary judgment was granted in favor of the alleged infringer, based on the conclusion that the claimed invention lacked utility and was therefore unpatentable under Section 101. The Federal Circuit reversed, relying on Manson for support. As correctly noted by the Federal Circuit:

> The threshold of utility **is not high**: An invention is useful under Section 101 if it is capable of providing **some identifiable benefit**. Emphasis supplied. 51 USPQ2d at 1702.

Given that the Federal Circuit specifically relied upon the Manson decision for support, these three words are dispositive to issues under Section 101: Some. Identifiable. Benefit.

In essence, a long line of well-grounded case law has established that under Section 101, the disclosure must merely provide an indication of usefulness of the invention – indeed, the threshold is so low under Section 101 that it is ***only*** when a claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end that a rejection can properly be applied, and sustained, under Section 101.

Applicants appreciate that the Guidelines are new; certainly, the Office appreciates that Section 101 is not new. If, as Deputy Assistant Commissioner Kunin points out in his article, the purpose of the Guidelines is to provide some insight to the PTO as to how to apply an analysis under Section 101, that purpose can be very useful for both the PTO and patent applicants. On this much the Office and Applicants can agree. However, the law has not changed, nor has the interpretation of Section 101. Thus, in the area of, *e.g.*, EST's (which as noted by Deputy Assistant Commissioner in his article, were an important impetus for the creation of the Guidelines), when the PTO opted to grant claims to EST's without the ability to limit the scope of such claims, it may have been important to provide a source of uniformity for utility under Section 101. As such, for a short DNA sequence that can often only be used as a probe, the legal utility for such a probe may be, indeed should be, very limited, such that, by implication, a claim to an EST will have a limited scope for an infringement analysis or during litigation. As can happen, and often does happen, one size does not fit all; unfortunately, the "default" approach to application of a guideline is to sometimes assume that if something does not readily fit within the parameters of a guideline, it must fail the requirements of the guideline.

With due respect, this is precisely what occurred several years ago during the examination of many biotechnology-based therapeutic compounds, where, based solely and exclusively on the predilections of certain PTO examiners/supervisors, the PTO simply refused to grant claims to any biotechnology invention claimed to have therapeutic utility in the absence of human clinical data. This approach was legally wrong. This approach was based upon the theory that unless an applicant could establish that a compound "worked" in humans, it was not patentable because absent human clinical data, the compound was allegedly not useful. Years of unnecessary and exceedingly costly battles were required before the PTO eventually recognized that this approach was legally incorrect, completely out of step with both logic and the law, and an unnecessary and inappropriate intrusion of individual-based reasoning on inventions and inventors who were often unable to push-back the bulk of the Federal Government.

But this eventual recognition came at the expense of hundreds of well-grounded claims that should have issued, but did not.

More than a mere academic problem, the lack of issuance of such claims was understood by the PTO as having a deleterious affect on the commercial opportunities for the inventors and assignees of such inventions – especially for the nascent biotechnology industry that absolutely relies upon patents for securing investment capital. Indeed, it is no accident that the PTO is under the umbrella of the Department of *Commerce*, given the critical role that patents play, and have played since the formation of our country, in commerce. Indeed, as precisely noted by the Supreme Court in Manson:

> A patent system must be related to the world of commerce rather than the realm of philosophy. 148 USPQ at 696.

When one thinks of "philosophical" discoveries that would fail under Section 101, these are generally related to abstract ideas, such as a perpetual motion machine and throw away utilities (*e.g.*, a transgenic animal serving as snake-food), or theories, such as $E=MC^2$. It is simply unacceptable to assume that because a forward thinking inventor defines an invention that does not readily lend itself to the confines of a set of guidelines, that suddenly, with government-sponsored "magic", an invention that pre-Guidelines fully conformed with Section 101, is somehow suspect post-Guidelines. With due respect, one questions the magnitude of philosophy in the process of defining the application of the Guidelines, and one further questions whether indeed, it is the mis-application of the Guidelines that ignores the relationship between our patent system and commerce.

In the present case, Applicants have, ***at a minimum***, fully disclosed some identifiable benefit for the claimed invention. Even under Section 112, which has a higher level of utility than Section 101, an applicant is not required to provide examples or evidence of all matters covered by a genus claim, so long as sufficient disclosure, coupled with ordinary skill, is provided as to how to make and use the claimed invention. Indeed, Applicants have provided examples of the use of the claimed invention by providing data that exemplifies the steps set forth in the claims -- how, then, can the Office assert that some identifiable benefit has not been provided, or that the specification does not provide the art with the ability to use the invention or that there is not a real world use for the invention. So oft-quoted is the following proposition that legal citation is superfluous: *a patent application is not intended to be a blueprint*!

Under Section 101, the utility threshold is not high. Here, Applicants have identified a problem that has plagued many institutions since the explosion of readily available and easily usable genetic tools have made accessible a plethora of receptor targets – how to exploit these targets for the betterment of the human condition. Applicants have disclosed, and the Watson Declaration makes clear, that the location and expression of a receptor are quite readily capable of determination and are useful tools to define insight into receptor function. Applicants have not focused on, nor do they claim, such function nor do they claim all orphan receptors. Rather, Applicants have discovered that by ignoring the art-directed focus on endogenous ligand discovery, and instead boldly moving in a unique direction towards constitutively active orphan receptors, one can, using, *e.g.*, the tools disclosed by Applicants, directly identify two functionally-defined types of compounds that can be directly identified using the constitutively active receptor: an inverse agonist or an agonist. These types of compounds have a recognized and well-defined meaning in the art (in addition to being defined in the specification) that are predicated upon a functional receptor response, and not mere receptor-binding. The mere selection of a receptor is based upon the needs of the artisan who reviews the application and uses her routine skill -- but once that selection has been made, Applicants' disclosure and teaching as to how to avoid the need for using an endogenous ligand for direct identification of a functional modulator of the receptor, *i.e.*, an inverse agonist or agonist, is quite valuable – and here, too, it is then a matter of mere selection by the artisan to determine if the needs of that artisan require an inverse agonist to reduce receptor function, or an agonist to enhance receptor function, these decisions being based upon the artisan's selection of a particular receptor of interest.

Applicants assert that they have not requested a mere "hunting license." Indeed, under both Manson and Orange Bang, the claimed invention has met the low threshold of Section 101 of providing ***some identifiable benefit***.

The Office simply can not, in good faith, maintain the position that under these facts, with these data, and with this disclosure, that the claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end. To maintain such a position, with due respect, is simply indicative of asserting a new, and as yet not well-defined set of nascent rules, over: the purpose of a patent; the legal requirements necessary to secure a patent; the well-defined body of case law developed since the enactment of the Patent Act of 1952; the commercial importance of patents; and, indeed, the basic quid pro quo fairness that our Nation's Founders established when they made the development of a United States patent system part of our U.S. Constitution.

To not withdrawal this rejection, with due respect, would be a travesty, not only on these facts, but also in light of the way that the Guidelines are being asserted.

PTO representatives have publicly stated in open forums to members of the patent community that because the PTO does not know exactly how to implement the Guidelines, it will reject most cases under Section 101 based upon the Guidelines and require applicants to define whether or not the Guidelines were properly invoked. This is, with due respect, governmental policy making at its absolute worst -- while the PTO tries to figure out what these Guidelines mean, **Guidelines *that the PTO drafted and implemented***, the customers of the PTO suffer -- greatly. This is not assisting applicants in getting their applications to issue. This is buck-passing of the most dubious type. This is not working with inventors. This is flaunting the power of Washington over assignees whose financial abilities hang in the balance. This is not leadership. This is hypocrisy wrapped within the multi-layered, protective sheath of the Federal Government. This is not re-inventing government. This is asserting the weight of the government over the needs of those who do play by the rules. We note for clarity: based upon Dr. Watson's extensive and well documented scientific background and the esteemed scientific reputation that he has established over the past twenty (20) years, his opinions must carry great weight, and in the absence of evidence to rebut Dr. Watson's opinions, or in the absence of an Examiner's opinion to the contrary, the rejections must be withdrawn. The Guidelines have served their intended purpose in this case by allowing the Office to provoke judicious evidence from Applicants, but they can not be maintained as a basis for a rejection under Section 101.

Withdrawal of this rejection is requested with respect -- to the extent that the foregoing section is considered or viewed as disrespectful, apologies are respectfully requested with the balanced understanding and request for due consideration in light of the frustrations that both the Examining Corp, as well as the patent bar, are experiencing with respect to the nascent and as yet, not fully defined Guidelines.

## X. Conclusion - Claims 1-18, 33-34 and 39-40 Are In Condition For Allowance

Applicants have amended the claims and submitted a formal drawing of Figure 12 to correct all informalities indicated by the Office. Applicants have submitted a Declaration by Dr. Watson in support of Applicants' position. Applicants have discussed the conformity of the claims with the new utility guidelines. In view of the foregoing, Applicants respectfully submit that claims 1-18, 33-34 and 39-40 and the Specification conform with the provisions of Section 112, and that claims 1-18, 33-34 and 39-40 are novel and patentable in view of the new Utility Guidelines.

Applicants authorize the Office to charge any deficiency or credit any overpayments to Deposit Account No. 50-1441.

Based upon the foregoing, Applicants submit that claims 1-18, 33-34 and 39-40 are in condition for allowance. If the Office requires any clarification or further information regarding the foregoing, Examiner Basi is kindly invited to contact Ms. Nguyen at his convenience at (858) 453-7200 x294.

Respectfully submitted,

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